

REMARKS

Entry of the foregoing amendments is respectfully requested.

Summary of Amendments

By the foregoing amendments claims 19-24 are cancelled and claims 37-56 are added, whereby claims 37-56 will be pending, with claims 37 and 55 being independent claims.

Support for the new claims can be found throughout the present specification and in particular, the original claims and pages 1, 13 and 15-17 of the specification.

Applicants emphasize that the cancellation of claims 19-24 is without prejudice or disclaimer, and Applicants expressly reserve the right to prosecute the cancelled claims in one or more continuation and/or divisional applications.

Summary of Office Action

Claims 19-24 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,595,373, claims 1-5 of U.S. Patent No. 6,121,243, claims 1-2 of U.S. Patent No. 6,562,794.

Claims 19-24 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for applying the flavonoid containing composition topically for treating an immunosuppressive condition caused by UV radiation, allegedly

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does not provide enablement for methods of preventing such immunosuppression of skin cells.

Claims 19-24 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Suzuki et al. U.S. Patent No. 5,145,781 (hereafter "SUZUKI") in view of Middleton et al., *The Flavonoids, Advances in Research Since 1986*, 1994, Chapman & Hill, London, Ch. 15, pp. 619-645 (hereafter "MIDDLETON"), and *Harrison's Principles of Internal Medicine*, 1994, New York, McGraw-Hill, Inc., 13th ed., pp. 309-313 (hereafter "HARRISON").

Response to Office Action

Reconsideration and withdrawal of the rejections of record are respectfully requested in view of the foregoing amendments and the following remarks.

Response to Obviousness-Type Double Patenting Rejection

Claims 19-24 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,595,373, claims 1-5 of U.S. Patent No. 6,121,243, claims 1-2 of U.S. Patent No. 6,562,794.

Applicants respectfully request that this rejection be held in abeyance until allowable subject matter has been indicated. Thereafter, Applicants will decide whether the filing of one or more Terminal Disclaimers is appropriate.

Response to Rejection of Claims under 35 U.S.C. § 112, First Paragraph

Claims 19-24 are rejected under 35 U.S.C. § 112, first paragraph, because the

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specification, while being enabling for applying the flavonoid containing composition topically for treating an immunosuppressive condition caused by UV radiation, allegedly does not provide enablement for methods of preventing such immunosuppression of skin cells.

Applicants respectfully submit that the claims submitted herewith do not recite the prevention of immunosuppression, wherefore this rejection is moot. At any rate, Applicants do not share the Examiner's opinion in this regard. In particular, the present Office Action concedes that the relative skill of those in the art is high. For this reason alone, one of ordinary skill in the art would be in a position to determine the prevention of immunosuppression by the claimed method, the more so since the present specification provides ample guidance in this regard. See, in particular the disclosure on pages 28-29 thereof.

Response to Rejection of Claims under 35 U.S.C. § 103(a)

Claims 19-24 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over SUZUKI in view of MIDDLETON and HARRISON. The rejection alleges that SUZUKI "meets all elements of the instant claims except that it fails to explicitly describe the use of α -glucosyl rutin use (sic) for immunosuppression of skin cells induced by UVB radiation." In this regard, the Office Action refers to MIDDLETON which allegedly shows a "plethora of information about the effects of flavonoids on immune system" and contends that in view thereof, it allegedly is within the purview of one of ordinary skill in the art to modulate the activity of the immune system by administering flavonoids of interest. HARRISON is relied on by the Examiner to show the alleged general knowledge in the art about the etiology of

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solar radiation and systemic response caused by UVB exposure. The rejection concludes that it would allegedly have been obvious to one of skill in the art to apply the formulation of SUZUKI topically and either treat or prophylactically treat patients in need of reversing the immunosuppression caused by UVB exposure because HARRISON allegedly teaches that such immunosuppression is dependent on the activity of T-lymphocytes and MIDDLETON allegedly teaches that T-lymphocytes can be controlled by topical administration of a flavonoid of choice.

Applicants respectfully traverse this rejection. In particular, a closer look at the documents cited in the present Office Action reveals that the allegations set forth therein are not supported by the cited documents.

For example, SUZUKI is directed to the preparation and uses of a single flavonoid, i.e., alpha-glycosyl rutin (see, e.g., title of SUZUKI). SUZUKI mentions that "alpha-glycosyl rutin is favorably usable as a yellow coloring agent, antioxidant, stabilizer, fading-preventing agent, quality-improving agent, preventive, remedy, uv-absorbent and deterioration-preventing agent in foods, beverages, tobaccos, cigarettes, feeds, pet foods, pharmaceuticals for susceptible diseases, cosmetics including skin-refining agent and skin-whitening agent, and plastics, in addition to the use in vitamin P-enriching agents" (see abstract of SUZUKI).

With respect to vitamin P it is stated in SUZUKI that "vitamin P takes part in some of the physiological activities of vitamin C in vivo; for example, in the hydroxylation of proline and lysine which are necessary to synthesize collagen as the main element of living connective tissues; the oxidation-reduction reaction of cytochrome C wherein Fe^{+++} is reduced into Fe^{++} ; and in the immunopotentiality via the increase of leukocyte". Col. 1,

lines 35-42. Accordingly, what SUZUKI teaches is that vitamin P (rutin) by itself does not have an effect on the immune system, but that it can support the effect of vitamin C in this respect. While this effect may be a favorable property of rutin (and alpha-glucosyl rutin), it is dependent on the presence of vitamin C, which cannot be expected to be present on the skin. Accordingly, one of ordinary skill in the art would not expect that (alpha-glucosyl) rutin has any (beneficial) effect on the immune system when it is applied topically as in the case of the method of the present invention. Accordingly, there is no expectation of success.

This is confirmed by, e.g., Example B-9 in col. 18 of SUZUKI. Example B-9 describes an ointment (i.e., a composition for topical application to the skin) which contains, *inter alia*, a significant amount of alpha-glucosyl rutin. In lines 15-18 of col. 18 SUZUKI states that this ointment “is antioxidative, highly stable, and favorably usable as a high-quality sun-screening, skin-refining agent, skin-whitening agent and promoter for healing injury and burn”. An effect of this ointment and in particular, of the alpha-glucosyl rutin component thereof on the immune system, let alone with respect to an immunosuppression caused by radiation, is neither taught nor suggested in SUZUKI.

Similarly, Examples B-14 and B-15 of SUZUKI describe formulations for topical application to the skin, i.e., a milky lotion and a cosmetic cream. Both products contain significant amounts of alpha-glucosyl rutin and, as in the case of the ointment of Example B-9, are stated to be “antioxidative, highly stable and favorably usable as a high-quality sun-screening, skin-refining agent and skin-whitening agent” and “antioxidative, highly stable and favorably usable as a high-quality santan (sic) cream, skin-refining agent and skin-whitening agent”, respectively. Again, these Examples do not mention any effect on the immune system, let alone a beneficial effect and in particular, a beneficial effect

attributable to the presence of alpha-glucosyl rutin.

In contrast, in Examples B-10 and B-11 of SUZUKI which describe injectable alpha-glucosyl rutin containing preparations it is mentioned that these preparations are “favorably usable in preventive and remedy for various diseases including viral diseases, bacterial diseases, circulatory diseases and malignant tumors”. Col. 18, lines 37-39 and 57-60.

Accordingly, even if one were to assume, *arguendo*, that the mentioning of “malignant tumors” in these Examples suggests the use of alpha-glucosyl rutin for the prevention and treatment of (any) immune conditions (which would be a quite far-fetched conclusion), SUZUKI certainly does not teach or suggest that any beneficial effect of alpha-glucosyl rutin on the immune system can be achieved by a topical application thereof.

To sum up, SUZUKI is concerned with a single flavonoid, i.e., alpha-glucosyl rutin, and does not teach or suggest any effect of this flavonoid on the immune system, let alone a preventive or curative effect with respect to UVB-induced immunosuppression. Even if one were to assume that the mentioning of “malignant tumors” in SUZUKI teaches or suggests a beneficial effect of alpha-glucosyl rutin on the immune system and, in particular with respect to UVB-induced immunosuppression, SUZUKI would not suggest that this effect can be achieved by topical application of alpha-glucosyl rutin.

MIDDLETON does not cure the deficiencies of SUZUKI. While it may be true that MIDDLETON makes reference to a large number of articles which report favorable results obtained with specific flavonoids, MIDDLETON does not teach or suggest that flavonoids in general or the flavonoids recited in the present claims in particular have a preventive or curative effect with respect to a specific condition, i.e., UVB-induced immunosuppression, let alone upon topical application of these flavonoids.

MIDDLETON itself makes it reasonably clear that one can not expect that results obtained with one specific flavonoid are obtainable with any other flavonoid as well. For example, in the middle of the right column at page 627 of MIDDLETON it is stated that "several more reports indicate the capacity of selected flavonoids to affect immune responses". Emphasis added.

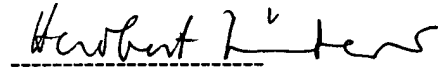
Applicants note that the rejection specifically relies on page 642 of MIDDLETON where the topical application of quercetin and its protective effect in mice with respect to the tumorigenesis caused by certain carcinogenic substances is discussed. However, the mechanisms proposed in this regard such as, e.g., inhibition of metabolic activation of the carcinogen, induction of enzymes involved in the detoxification of the carcinogen and binding to reactive forms of the carcinogen, have nothing to do with immunosuppression, let alone with UVB (radiation)-induced immunosuppression. In this regard, it is noted that the present rejection alleges that HARRISON teaches that "the immunosuppression caused by UV-B is caused by the induction of suppressor T cells throughout the body". Page 7, next-to-last paragraph of Office Action. Clearly, one of ordinary skill in the art would not conclude that the mechanisms discussed in MIDDLETON are effective for the prevention of the induction of suppressor T cells.

Applicants submit that for at least all of the foregoing reasons, a combination of the teachings of SUZUKI with those of MIDDLETON and HARRISON is unable to render obvious the subject matter of any of the claims submitted herewith. Accordingly, withdrawal of the claim rejection under 35 U.S.C. § 103(a) is warranted and respectfully requested.

CONCLUSION

In view of the foregoing, it is believed that all of the claims in this application are in condition for allowance, which action is respectfully requested. If any issues yet remain which can be resolved by a telephone conference, the Examiner is respectfully invited to contact the undersigned at the telephone number below.

Respectfully submitted,
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